Influence of baroreflex on volume elasticity of heart and aorta in the rabbit

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Wronski, T., E. Seeliger, P. B. Persson, A. Harnath, and B. Flemming. Influence of baroreflex on volume elasticity of heart and aorta in the rabbit. Am J Physiol Regulatory Integrative Comp Physiol 282: R842–R849, 2002; 10.1152/ajpregu.00474.2001.—Optimal ventriculoaortic coupling includes tuning of elastic properties. The ratio of effective arterial elastance and left ventricular endsystolic elastance is often taken as a measure for mechanical and energetical efficiency. The present study determined the time course of ventricular and aortic volume elasticity (VE = dp/dV) throughout a complete heartbeat. This was achieved by using changes of eigenfrequency of two catheter-transducer systems under closed chest conditions in rabbits. Short-term VE modulation was studied by a baroreflex response, as induced by pressure changes applied to the carotid sinus. Long-term changes were studied in atherosclerotic rabbits (12 wk of high-cholesterol feeding). The time course and mean values of ventricular and aortic VE were changed by the baroreflex stimulus. Cholesterol feeding diminished the response. The degree of ventriculoaortic coupling, as quantified by VEAorta/VEVentricle ratio, varied during a single ejection period. The large span allows either maximal energetical efficiency or maximal stroke work. Although normal rabbits adjusted their ventriculoaortic coupling during baroreflex input, the cholesterol-fed rabbits failed to do so.

ELASTIC PROPERTIES OF LARGE arteries, especially that of the aorta, influence various elements of the cardiovascular system. Due to elastic distension, these vessels store ~50% of stroke volume during systole to deliver it toward the periphery during diastole. This systolic-diastolic interplay does not only impinge on peripheral circulation. It also impinges on the heart, e.g., by modifying blood pressure, coronary blood flow, and relaxation of the ventricle (6). Systolic-diastolic interplay is not merely determined by properties of the ventricle, but also by the volume elasticity (VE = dp/dV) of the vessels. Arterial VE changes with aging, and it is altered by atherosclerosis, hypertension (6), and by altered function of vascular smooth muscles.

Thus functional coupling of left ventricle and large arteries is a determinant of hemodynamic performance of the cardiovascular system. In addition, this coupling influences energetical performance (17). For instance, increasing arterial VE by means of an artificial conduit increases myocardial oxygen consumption markedly, whereas hemodynamic performance is barely altered (23). Ventriculoarterial coupling has been described quantitatively by the ratio of arterial elastance (Ea) to left ventricular endsystolic elastance (Ees) (13, 37) or by the reciprocal ratio (29).

The baroreflex system is well known to stabilize arterial pressure (15, 22, 33). In addition, it has been recognized to be an important mechanism in tuning the heart and vasculature, i.e., in tuning their volume elasticity (VE) (37). Both ventricular and arterial VE are influenced by carotid baroreceptors (25). Thus it has been assumed that the baroreflex is designed to regulate the ventricular and arterial properties to optimize the energy transmission from left ventricle to the arterial system (25). However, conflicting results have been obtained regarding the influence of baroreceptors on arterial compliance (11).

This may, in part, rely on several different methodical approaches to describe elastic properties of vessels (12). A vast number of parameters has been defined, thus the literature is confusing (34). Most methods have in common that the description of elastic properties is limited to one average value representing one or several complete heartbeats. However, the volume-pressure relationship of vessels is nonlinear, thus these methods may not be appropriate. Time courses of VE or compliance during one heartbeat have occasionally been reported (7, 26, 30, 39). Recently, we reported a new method that allows simultaneous determination of ventricular VE and aortic VE with a resolution of six 40-ms mean values per systole and six 40-ms mean values per diastole (41). The method is based on the modulation of the eigenfrequency of a modified catheter-pressure transducer system. In the present study, this method was improved to yield momentary measures instead of 40-ms mean values.

This study aims to determine the impact of baroreceptor stimulation, and the impact of changes in ventricular and aortic pressures induced by this stimulation, on the time course of ventricular and aortic VE. The experiments were performed in two groups of rabbits. One group was fed a normal diet. The other

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group received a high-cholesterol diet to induce atherosclerosis, which by structural as well as functional alterations, it is assumed to elicit changes of VE (14, 18, 20, 31, 32, 35, 40, 42).

**MATERIALS AND METHODS**

**Experimental groups.** Rabbits, 4 mo of age, of both genders were used. They had access to food and water ad libitum. The control group \( n = 5 \) was fed a standard pellet diet. The experimental group \( n = 9 \) received a daily 120-g ration consisting of a standard pellet mixture with added 20 ml of sunflower oil and 2 g of cholesterol. Cholesterol feeding was maintained for 12 wk and was terminated 2 wk before the experiment.

**Surgical procedures.** This investigation conforms with the Guiding Principles for Research Involving Animals and Human Beings published in *Am J Physiol Regulatory Integrative Comp Physiol* 280: R1913, 2001. Rabbits were anesthetized with intravenous \( \alpha \)-chloralose (60 mg/kg) and urethane (200 mg/kg). Rectal temperature was maintained between 37 and 38°C by a thermostat table. The trachea was cannulated via tracheotomy; each animal breathed spontaneously throughout the experiments. After surgery, the animal was placed in a supine position. A constant-flow infusion pump was connected to a cannula placed into the right brachial vein. An infusion of a mixture of 180 mmol/l of glucose and 180 mmol/l of mannitol at 0.12 ml/min was used to maintain constant plasma volume and osmolality. A catheter with a length of 15 cm and an outer diameter of 2.5 mm was inserted into the left ventricle via the left carotid artery. An aortic catheter with similar dimensions was positioned via the brachial artery.

Isolated perfusion of carotid arteries (short-segment upstream and downstreams of the carotid bifurcation) of both sides was used to induce pressure changes to the carotid baroreceptors. Left and right common carotid arteries were cannulated upstream of the carotid glomera (downstream insertion of left ventricular catheter) and connected to an extracorporal circuit system, which through blood from the cannulated left femoral artery flowed. The extracorporal system consisted of a roller pump, a blood filter, and a chamber for application of pressure oscillations. This cylindrical chamber was divided into two compartments by a rubber membrane. One compartment (blood compartment) was part of the extracorporal circuit. The other one was filled with saline and connected by a rigid tube to a second chamber attached to a electromechanical oscillator system (ESE 201, Meßelektronik Dresden, Germany). The oscillator was driven by the output of a sine wave generator, which was amplified by a power amplifier (LV 101, Metra Radebeul, Germany). Pressure oscillations of 15-mmHg amplitude and constant frequency of 4 Hz were superimposed onto the mean perfusion pressure of the extracorporal circuit. Downstream of the carotid glomera, left and right external carotid arteries were cannulated. Blood flowed through a Starling resistor into the left jugular vein. By means of the Starling resistor, mean perfusion pressure of the extracorporal circuit and thus of the carotid artery pressure \( p_c \) could be varied. \( p_c \) was continuously measured by a pressure transducer (Siemens Elema). The applied changes of \( p_c \) were used to induce reflex responses of the systemic circulation. The levels of \( p_c \) decrease and \( p_c \) increase were chosen according to the individual rabbit’s mean systemic arterial pressure \( p_a \) immediately before the respective \( p_c \) change. The protocol of \( p_c \) changes was as follows: 1) mean value \( p_a = \) mean value \( p_c \); 2) \( p_c \) increase by 10 mmHg; 3) mean value \( p_a = \) mean value \( p_c \); 4) \( p_c \) decrease by 10 mmHg; 5) mean value \( p_a = \) mean value \( p_c \); 6) \( p_c \) increase by 30 mmHg; and 7) mean value \( p_a = \) mean value \( p_c \). To prevent reflex influences exerted by aortic baroreceptors and cardiac mechanoreceptors, both vagal nerves were cut.

**Measurements.** Left ventricular pressure \( p_{lv} \) and aortic pressure \( p_a \) were continuously measured with pressure transducers (Siemens Elema). Analog-to-digital conversion was performed at a rate of 1,000 Hz and an accuracy of 12 bits.

To obtain VE measurements of the left ventricle and aorta by use of the catheter-transducer system, VE coefficients of the transducers were lowered below 30,000 mmHg/ml by means of fluid-filled chambers attached to the respective transducer (41). This reduces the eigenfrequency of the catheter-transducer system. Under these conditions, the steep pressure increments and decrements of left ventricular and aortic pressures cause eigenoscillations with amplitudes up to 40 mmHg at the beginning. Oscillation amplitudes smaller than 5 mmHg were excluded because the accuracy of the method would decrease.

These eigenoscillations are superimposed onto \( p_{lv} \) during the ejection phase and filling phase and to \( p_a \) during systole and diastole. The frequency and dampening of the oscillations depend, on the one hand, on the intrinsic characteristics of the catheter-transducer system. On the other hand, they also rely on elastic and viscous properties of the left ventricle and aorta. Changes of these properties during the ejection and filling phases result in modulations of frequency and/or dampening of the eigenoscillations. For details of the theoretical background and calibration of the method, see Ref. 41.

**Data analysis.** \( p_{lv} \) was separated from the superimposed eigenoscillations as described in Ref. 41. The following differential equations were used

\[
m \frac{dq_1}{dt} + r \frac{q_1}{q_1} + E' \frac{q_2}{q_2} \frac{dt}{E'} - E' \frac{q_1}{q_1} \frac{dt}{r q_1} = 0 \quad (1a)
\]

\[
E' \frac{q_1}{q_1} \frac{dt}{r q_1} + M \frac{dq_1}{dt} + Z q_1 \frac{dt}{q_2} = 0 \quad (1b)
\]

with \( E: \) VE of the transducer; \( E': \) VE of the hollow body; \( M: \) effective mass of the catheter; \( m: \) effective mass of the coupled vessel; \( Z: \) friction resistance of the catheter; \( r': \) resulting viscous resistance of the heart and aorta; \( q_1: \) oscillatory flow in the catheter; and \( q_2: \) oscillatory flow between the heart and aorta.

This system of differential equations (Eq. 1a and Eq. 1b) describes the oscillatory behavior of a catheter-transducer system consisting of \( E, M, \) and \( Z, \) which is connected with a hollow body \( T \) with the yet unknown VE \( E'. \) The system of differential equations is one with constant coefficients, i.e., the calculated coefficients are independent from time. To take a possible time dependency of coefficients \( E' \) and \( r' \) into account, in our previous paper (41), out of a complete damped oscillation observed throughout the whole systole and diastole, fractions of 40-ns duration were taken, and the equation system was solved for these fractions. Then the time window was shifted in steps of 10 ms to estimate the coefficients throughout the ejection and filling phases. Thus the calculated VE in Ref. 41 represents 40-ns mean values, which precludes assessment of faster changes. To allow as-
Assessment of instantaneous VE changes, the following modification in calculating VE was used in the present paper. $E'$ and $r'$ in Eqs. 1a and 1b were replaced by the functions $E'(t)$ and $r'(t)$ using a fourth-order polynomial.

$$E'(t) = E' + a_1 t + a_2 t^2 + a_3 t^3 + a_4 t^4$$
$$r'(t) = r' + b_1 t + b_2 t^2 + b_3 t^3 + b_4 t^4$$

(2)

The complete damped oscillation is fitted, and, in addition to the parameters described above, parameters $a_1$ to $a_4$ and $b_1$ to $b_4$ are calculated. A fourth-grade polynome was chosen, because it allows accurate fitting of most possible time courses of $E'$ and $r'$ throughout a systole or diastole. One exception would be extremely short peaks within the time course. However, such peaks would be visible as quick frequency alterations within the original signal, which did not occur.

Statistical analysis. The heartbeats from each animal were analyzed during at least one complete respiratory cycle. All data of a heart cycle were normalized to yield a standardized data of a heart cycle were normalized to yield a standardized

regular and aortic VE during equilibrated conditions (pc = pa), as depicted in Fig. 1B, is amplified when pc is reduced by $-10$ mmHg (Fig. 2C). However, with a pc increase of $+10$ mmHg, this time course is changed: VE continues to decrease throughout the systole. In addition, the decrease of aortic VE during the first half of the systole (Fig. 1C) is almost completely abolished during both the increase and decrease of pc (Fig. 2E). However, the sharp decrease of aortic VE from end-systolic to early diastolic values is preserved. In the cholesterol group, changing pc did not result in clear-cut changes of VE time courses.

Figure 3 depicts the relationship between pressure and VE during one heartbeat, as well as the influence of pc changes on the relationship. Thus, for an individual control rabbit, ventricular VE is depicted over ventricular pressure (Fig. 3A) as is aortic VE over aortic pressure (Fig. 3B). From these plots, it becomes clear that at the same pressure, different VEs are observed, even under equilibrated conditions (pc = pa). Increasing pc by 10 mmHg shifted the locus curves along the pressure axis as well as the VE axis. Over a wide range of pressure, VE values at a certain pressure differed markedly. As indicated by the vertical lines, up to four different VEs were observed at the same pressure value.

Adaptation of aortic elastic properties to left ventricular elastic properties during systole is considered an important element in reducing the heart’s energy requirements (23). Therefore, the time course of the ratio $V_{aortic}/V_{ventricle}$ was calculated in Fig. 4. In controls (Fig. 4A), the ratio was markedly influenced by pc changes: pc elevation increased the ratio during the second half of the systole, whereas pc decrease had the opposite effect. No significant changes were observed in the cholesterol group (Fig. 4B).

DISCUSSION

The main findings of this study are that ventricular and aortic VE change markedly within one heartbeat.
The time course and mean values of VE are changed by baroreflex input. Differences in the time course do not simply reflect passive changes, e.g., due to changed pressure, but they rely on active adjustments of wall properties induced by the baroreflex. Cholesterol feeding diminishes the response of ventricular and aortic VE to baroreflex input. The degree of ventriculoaortic coupling, as quantified by $V_{E_{aorta}}/V_{E_{ventricle}}$ ratio, varies during a single ejection period, starting from a range assumed to represent maximal efficiency to a range of maximal stroke work. Although control animals changed ventriculoaortic coupling during baroreflex input, the cholesterol-fed rabbits failed to do so.
During volume propulsion within the circulation, e.g., from the left ventricle into the aorta, high mechanical as well as energetical efficiency is achieved. In the pioneer work to obtain ventriculoaortic coupling, $E_a$ and ventricular $E_{es}$ were derived. Then $E_a/E_{es}$ was calculated (13, 37). Only one value of $E_a/E_{es}$ per heart cycle was obtained. The present study describes the time courses of ventriculoaortic tuning ($VE_{aorta}/VE_{ventricle}$; Fig. 4) throughout the heart cycle. This quotient changes rapidly during the systole. The changes of the quotient $VE_{aorta}/VE_{ventricle}$ result from alterations in VEs of both compartments (Fig. 1), i.e., the ventricle and the aorta.

**Time course of aortic and ventricular VE.** Venticular and aortic VE change during the systole and diastole, i.e., within 100 ms (Figs. 1 and 2). Every decrease of VE of a given vessel toward which volume is propelled results in a pressure decrease in this vessel. Accordingly, the driving pressure difference increases, and thus it increases the fluid flow.

The time course of aortic VE during systole and diastole (Figs. 1 and 2) cannot be accounted for by rapid vascular smooth muscle contraction, which is too sluggish. Instead, vessel geometry is important. With increasing volume, VE of a given hollow body decreases in a nonlinear fashion (34). If the wall’s material is in accordance with Hooke’s law, then VE is $-1/r^3$ (radius of the vessel). Moreover, the passive tension-length relationship of isolated vessel or heart preparations is best fitted to an exponential curve (38). For small volumes, the dependency of VE on volume is great, whereas the dependency of VE on the modulus of elasticity is meager. Thus stretching results in a decrease of VE. For a larger initial volume, the opposite is valid. With intermediate initial volume, a biphasic behavior of VE results, just as it is observed in aortic VE of control rabbits during systole (Fig. 1). Similar to VE, viscous resistance of the aorta changes in a biphasic manner during the systole (Fig. 1E). Vessel wall viscosity has been measured under different physiological conditions (2, 9, 10, 30). It is conceivable that changes of viscosity are attributable to the factors described in detail for VE.

**Left ventricular VE of control rabbits increased during the systole,** from $80 \text{ mmHg/ml}$ in early systole to $100 \text{ mmHg/ml}$ in late systole (Fig. 1B). Although decreasing ventricular volume is assumed to be the major reason for this VE increase, changes of wall thickness and ventricular geometry may also have contributed.

The decrease of $VE_{aorta}$ in the early systole (Fig. 1C) may rely on distension of the aorta. During the second part of the systole, flow from the ventricle tapers off and release of stored blood starts. Thus VE increases. This decrease of aortic VE observed in early systole supports ejection, as has been described by Berger and Li (7) as well as MacWilliams et al. (30). According to Kolh et al. (24), this results in both an increase in ejection volume and a decrease in energy demand.

**Influence of baroreflex.** The baroreflex system is assumed to play a decisive role in optimizing ventriculoarterial coupling (25, 37). With an increase of carotid...
perfusion pressure (pc), the reduced inotropic influence results in a decrease of ventricular VE during late systole. With decreasing pc, the opposite is observed (Fig. 2C). In control rabbits, the changes of aortic VE during the systole (Fig. 2E) induced by an increase and decrease of pc, respectively, are not symmetrical when related to the control curve (pc = pa). When pc increases, vascular smooth muscles relax. Thus VE of the aorta probably does not reflect muscular but rather collagen elements of the wall. This “paradoxical” behavior of vessels has been described before (21). In addition, elevation of pc decreases systemic pressure, which would reduce vessel diameters, and, because of the volume dependency of VE, would also increase VE. At present, the relative contributions of these different mechanisms cannot be assessed. As depicted in Fig. 2, changes in pc result in alterations of the time course of both ventricular and aortic VEs during the normalized heartbeat. Different VE values at the same time of the heartbeat, however, do not allow to distinguish whether these VE changes are brought about by either active or passive mechanisms. Therefore, in Fig. 3, ventricular and aortic VE values of one control rabbit were related to the respective values of plv and pa. If the heart or aorta would display pure elastic properties, then only one VE value would be observed at a given pressure. If viscoelastic properties are taken into account, then two VE values at a given pressure would be found. The observation that more than two different VE values occurred at several distinct values of pressure indicates that the baroreflex induced an active adjustment in VE.

**Influence of cholesterol.** As previously reported (16), cholesterol feeding of comparable dosage and time courses does not change ventricular and aortic pressures (Fig. 1A). However, the sensitivity of arterial chemoreceptors and baroreceptors is altered (1, 16, 27). Alteration of baroreflex sensitivity due to cholesterol feeding is confirmed by the present results.

Cholesterol feeding is known to result in marked changes of various elements that contribute to VE of vessels. For example, cholesterol content of elastic and collagen fibers and within the vessel’s intima increases (40). Several reports indicate that the distensibility of the aortic wall is reduced by cholesterol feeding (14). In contrast to VE, however, distensibility is independent of volume. This distinction may be of particular relevance with regard to effects of cholesterol feeding, because cholesterol feeding has been shown to increase aortic volume (27). The increase in aortic volume may

![Fig. 3](image-url)  
**Fig. 3.** VE – pressure loops (locus curves) for 1 control animal during 2 complete cardiac cycles: 1) during equilibrated conditions (arterial pressure (pa) = pc) and 2) during pc + 10 mmHg. A: left ventricular VE – pressure loop. B: aortic VE – pressure loop. Starting and ending points are shaded. Numbers indicate time within the normalized beat as shown in Figs. 1 and 2, last systolic and first diastolic values are connected by dotted lines. Thick vertical lines indicate that up to 4 different VEs were observed at the same pressure value.

![Fig. 4](image-url)  
**Fig. 4.** Influence of changes in pc on systolic time course of the ratio VEaorta/VEventricle for cholesterol group (n = 5; A) and cholesterol group (n = 9; B). Pc changes depicted here were +10 and −10 mmHg for control animals and +30 and −10 mmHg for cholesterol-fed animals. *Significant differences (P < 0.05) for equilibrated conditions (pa = pc) vs. changed pc. **Significant differences (P < 0.05) for pc +10 mmHg and pc −10 mmHg.
compensate the decrease in distensibility. In accordance with this hypothesis, comparison between the average VE values of a total heart cycle between cholesterol rabbits and control rabbits did not reveal differences in the present study. However, there were differences between the groups with regard to the time course. Aortic VE of cholesterol-fed rabbits increased continuously with stretching during early systole, i.e., during storage of volume. This effect is probably related to the higher initial volume and an increase in the modulus of elasticity.

In addition, aortic VE during the diastole was generally higher in the cholesterol group. From studies using the time decay procedure to assess aortic compliance or elastance, it was concluded that cholesterol feeding reduces the aortic compliance. With regard to our diastolic VE, the present results confirm this notion (4, 5, 8, 11).

In addition to structural alterations of passive wall elements, cholesterol feeding also results in marked changes in the active element, namely, vascular smooth muscle contraction. This is due to multiple humoral (19, 31) and structural changes (35). In the face of these multiple alterations of systems determining the tone of smooth muscle, it is somewhat surprising to note that cholesterol feeding resulted only in relatively small changes in aortic VE during control conditions (pc = pa).

As mentioned above, however, the baroreflex response was markedly diminished in cholesterol-fed rabbits (Fig. 2B). As has been previously reported (16, 27), this may be related to alterations in several components of this feedback loop, including alterations of vessel reactivity. The reduction of baroreflex sensitivity in cholesterol-fed rabbits was marked: to induce a comparable aortic and ventricular pressure change in control rabbits, a threefold greater increase of pc was required (30 mmHg). In addition, ventricular and aortic VE did not respond to pc changes in these rabbits, despite the stronger stimulus used (pc decrease by 30 mmHg). It is concluded that the cardiovascular system has reached a stable state. Obviously, it can no longer respond to baroreceptor stimulation with adequate regulation.

**Ventriculoarterial coupling.** The relationship between the elastic parameters effective Ea (Ea = pa/stroke volume) and ventricular Ees has been studied in a variety of physiological and pathophysiological conditions (3, 18, 36). According to Burkhoff and Sagawa (13), the heart’s stroke work becomes maximal at the expense of increased oxygen consumption, when Ea = Ees. The heart’s work is particularly efficient, when the ratio of stroke work to oxygen consumption is greatest, as it is at an Ea/Ees ratio of ~0.7.

Little and Cheng (29) reported that within a range of Ees/Ea ratio from 0.56 through 2.29 (equal to Ea/Ees ratio 0.44–1.7), stroke work is lowered by 20% below its maximum only. Thus stroke volume displays a plateau over a fairly large range of Ea/Ees ratios.

In Fig. 4A, the systolic time course of the ratio VE_{Aorta}/VE_{Ventricle} of control rabbits is depicted. During control conditions (pc = pa), the ratio varies between 0.7 and 1. When pc is increased by 10 mmHg, the ratio becomes greater, reaching peak values of 1.4. As depicted in Fig. 2E, this increase of VE_{Aorta}/VE_{Ventricle} mainly relies on an increase of aortic VE. The ratio becomes slightly lower when pc is decreased. In cholesterol-fed rabbits (Fig. 4B), the ratio did not change significantly to altered pc, an effect probably attributable to the lowered reactivity of the aorta as discussed above.

Despite the different methods used, the magnitude of the ratio VE_{Aorta}/VE_{Ventricle} in this study resembles that of the Ea/Ees ratio (13). If we follow the interpretation of Burkhoff and Sagawa (13), then the cardiovascular system of our control rabbits would work within the range of maximal efficiency during early systole, whereas it approaches the point of maximal stroke work at late systole. A decrease of pc results in a shift of the ratio toward higher efficiency, whereas an increase of pc had the opposite effect, i.e., the ratio was well above one in late systole. However, this ratio would still be within the plateau range defined by Little and Cheng (28), i.e., stroke work is assumed to be reduced by 20% or less only.

**REFERENCES**


